## Innovative surgical approach for rectal cancer

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## General summary and discussion

The aim of this thesis was to describe the first short-to-medium term outcomes after transanal total mesorectal excision (TaTME) in the early phase of implementation of this new technique as a surgical treatment for patients with rectal cancer. TaTME was introduced as an alternative to laparoscopic surgery with potentially better short-term postoperative outcomes as a result of less inflicted trauma during the procedure, as well as possible improved surgical quality because of direct visualisation of the tumour and therefore improved pathological outcomes. Gelderse Vallei hospital was the first to perform TaTME procedure in the Netherlands. In affiliation with the VU medical centre, they published their first experience of TaTME to show the feasibility and safety of this procedure in 2013.[1] As the TaTME procedure includes an 'iatrogenic' perforation of the rectum, which can lead to bacterial contamination and potentially result in intra-abdominal infections, we investigated the intra-abdominal bacterial contamination in 2014 *(chapter 2)*. The study shows that all patients with a presacral abscess had a positive perioperative culture. None of the patients with a negative culture developed abscesses. This implicates that when the purse string suture is made, bacterial contamination is at risk. However, there are no comparative data on bacterial cultures after laparoscopic TME surgery, hence drawing a meaningful comparison between the two techniques based on this particular element proves difficult. In *chapter 3* we describe the experience of the first 80 TaTME procedures in VU medical centre and Gelderse Vallei hospital. In this series we reported severe complications in 11% of patients, which is similar to complications reported after laparoscopic TME (suggesting that the risk of bacterial contamination might be equally high in both procedures). However, at time of writing povidone-iodine is still used in TaTME after the purse string suture is performed.



Although the majority of steps of the procedure remained unchanged as the technique evolved, several steps were adjusted. As such, the surgeon initially started with the transanal phase followed by the laparoscopic phase in implementation of the procedure. Moreover, we changed the procedure from a one-team to a two-team procedure as firstly described by Lacy et al.[2]

With the lack of randomised controlled trials to prove the non-inferiority of TaTME compared to laparoscopic TME, several cohort studies were published in order to show feasibility and safety of TaTME. We therefore performed a systematic review of these data *(chapter 5)*. After a literature search, 165 articles were screened for full-text review of which 33 articles with a total of 794 patients could be included for analyses. Conversion rate was reported in 3.0%, major complications in 11.5% and 30-day mortality in 0.3% of cases, numbers all comparable to or better than reported after laparoscopy.[3] When comparing low-volume centres (≤30 cases) with high-volume centres (>30 cases), although p-values could not be measured, conversion rate and postoperative complications

were better in high-volume centres, implicating an important learning curve effect on these outcomes.

With this knowledge, *chapter 9* describes the learning curve of the first 138 patients in Gelderse Vallei hospital, the first hospital in the Netherlands where TaTME was performed. Laparoscopic colon surgery has been proven to result in less postoperative complications and conversions after increased experience.[4,5] With the introduction of a new technique as complex and challenging as TaTME, it was therefore of paramount importance to evaluate the learning curve of this procedure. The learning curve evaluation conducted, reported a significant decrease in overall complication rate and major complication rate after the first 40 patients, suggesting that surgeons have to perform at least 40 cases in order to reach competency, based on acceptable postoperative morbidity. Even though the technique is considered more difficult than laparoscopic surgery, a minimum of 40 cases is less than the number of cases reported in the literature for the conventional technique with figures ranging from 50 to 100 cases. Furthermore, the study showed a significant decrease in operating time and conversion rate when comparing a one-team with a two-team approach with a mean difference of 42.4 minutes (range 28.8-60.0, $p<0.001$). Although these results are based on a single centre experience, it is one of the largest cohorts of TaTME researching learning curve published at time of writing.

Acknowledging the fact that a learning curve for TaTME exists, and surgical training can be utilised to shorten this learning curve, a collaborative of surgeons in the Netherlands came up with a structured training pathway. This pathway includes a multi-step program of e-learning, didactic courses, detailed anatomy instruction, observation of a TaTME live procedure, a hands-on cadaver workshop and proctoring of the first cases by TaTME experts. The effectiveness and safety of this training pathway, including the number of major complications, have been assessed as part of this thesis *(chapter 10)*. In total, 120 patients who were operated in these training centres were included in the study. Mean operative time was 293 minutes and intraoperative complications were reported in six patients (4.9%), which is less than reported in current literature. Although intraoperative complications were low, postoperative complications according to Clavien-Dindo were substantial. In 19.2% of patients, complications were graded as IIIa or IIIb. A primary anastomosis was performed in 98 cases (81.7%) of whom 17.3% encountered anastomotic problems. Although similar results were found in the first 40 patients of the learning curve study (27.5% which in later stage dropped to 5%), these numbers are considerably high, taking into account the advantages of the TaTME technique. Leakages and/or presacral abscesses may potentially emerge as a consequence of the open rectal stump and bacterial contamination as demonstrated in *chapter 2*. A limiting factor in this study was that a mere maximum of the first ten consecutive patients per

centre could be included in order to specifically evaluate the quality and safety of the initiation of TaTME within this pathway. When comparing the first five with the sequential five patients per centre no significant differences were measured in postoperative outcomes. However, as previously described in our learning curve study, it is likely that significant differences will materialise after 40 cases have been performed.

Postoperative morbidity is one of the most important outcomes that should be analysed at the beginning of implementation to show the feasibility and safety of a new surgical technique. However, pathological outcome in terms of completeness of mesorectum and involvement of circumferential resection margin (CRM) is perceived to be of great influence on recurrence and survival rates for patients after rectal cancer surgery.[6,7] *Chapter 3 and 4* reported complete or nearly complete specimens in respectively 97% and 100% of cases, which is comparable to rates after laparoscopic rectal surgery. The same can be said about CRM involvement, respectively 2.5% and 3.1%, which is much better compared to outcomes after laparoscopic approach (10%). Our systematic review *(chapter 5)* reported percentages similar to these rates with complete or nearly complete specimens in 98.3% and 95.6% and positive CRM in 4.5% and 4.8% of cases in respectively high-volume centres and low-volume centres. Our study of a structured training pathway did not report any incomplete specimen in 120 patients *(chapter 10)*. Current consensus is that these promising outcomes are a result of the improved visualisation in endoscopic transanal approach, which leads to improved surgical quality. Nevertheless, as TaTME has only been introduced in 2012, no long-term outcomes with regard to survival and recurrence rates have been demonstrated yet.
In spite of the current lack of evidence of expected long-term outcomes such as less recurrence, evidence exists that underlines the relevance of a complete resection of the total mesorectum: data from the Dutch TME trial shows that incomplete specimen is associated with an increased risk for local and distant recurrence. Although pathology report is the gold standard to assess the completeness of mesorectum after total mesorectal excision, *chapter 4* gives us insight in the completeness of mesorectum measured by postoperative MRI. We found that residual mesorectum was left behind in patients in 46.9% following laparoscopy compared to 3.1% following TaTME ($p<0.001$). Because of the small sample size, analysis of relation between completeness of mesorectum on MRI and pathology assessment could not occur and follow-up was done within too short a time frame to establish recurrence rates. However, these results suggest that pathology assessment might not be fully adequate in assessing whether a complete mesorectal excision has been performed.

TaTME might be superior over laparoscopic TME when analysing short-term oncological outcomes by performing a more complete mesorectal excision. The anatomy of the mesorectum suggests,

that in order to perform a true complete mesorectal excision, the surgeon needs to operate as distal as possible. Theoretically as performing transanal TME, instead of laparoscopic TME, allows for better visualisation, less damage to the neurovascular plexus could occur with improved functional outcomes as a result. Moreover, because of the transanal surgical approach in TME, most distal tumours can be resected without the need for a permanent stoma, resulting in more low anastomoses compared to a laparoscopic approach. In our study about residual mesorectum on MRI *(chapter 4)* height of anastomoses differed significantly between the laparoscopic and transanal group (7.3cm vs 4.7cm respectively, p<0.001). However, lower anastomoses can influence functional outcomes and quality of life negatively. *Chapter 6* provides us with results on quality of life and functional outcomes after TaTME compared to laparoscopic TME. Unfortunately, no data on tumour height could be measured in this series. Although it is a retrospective study with a significant difference in follow-up, groups were comparable in almost all baseline characteristics. The study shows that anal dysfunction in terms of LARS (low anterior resection syndrome) occurs after both laparoscopic and transanal TME, comparable to published literature. At time of writing, data on functional outcomes after TaTME remains scarce and this hiatus needs to be addressed in future research.

With transanal TME, as previously described, the complete rectum is removed which is the only way for radical surgery in rectal cancer. The only exception to this rule applies to patients with low-risk T1-rectal cancer, well- to moderately differentiated, no lymphangio- or vaso-invasive growth, diameter <3cm, including tumour free margins. For this group of patients, a local excision by means of transanal endoscopic microsurgery (TEM) suffices. In 2012 we described the introduction of the TAMIS (transanal minimally invasive surgery)-platform: a flexible access port using standard laparoscopic instruments which could potentially replace the TEM procedure, in which a rigid proctoscope is used. *Chapter* 8 shows us the current status of this platform ever since its implementation. Nevertheless, although the TAMIS platform is a more economically efficient method and is easy to use, several cohort studies - although small - have shown that the quality of the local resection, risk of postoperative complications as well as functional and oncological outcomes are comparable in both techniques. Hence, although the flexible access port has not replaced the rigid proctoscope, it has contributed to the development of new rectum sparing techniques that are aimed at improving quality of life while maintaining oncological quality. Moreover, the flexible entry-point has become an essential part of the 'step-up-approach' for rectal carcinoma, in order to determine whether radical surgery is required or not, and hence contributes to avoiding over-treatment. The latter is of particular importance since the 2014 introduction of population screening of colorectal carcinoma which has led to an increased incidence of big adenomas and early carcinomas.

Although over-treatment is tried to be avoided, in 40% of patients after local excision, pathology reports reveal a high-risk T1 or more invasive rectal cancer than initially thought. In these patients, completion radical surgery by total mesorectal excision (cTME) is advised, as the risk of local recurrence is significantly higher after local excision only. However, this strategy has potential adverse outcomes: completion surgery is reported to be more difficult because of weakened integrity of the rectal wall due to inflammatory change or fibrosis at the previous excision site, which could lead to a poorer TME specimen quality. Transanal TME could be advantageous in cases with a high-risk T1 after local excision, because of the combined laparoscopic and transanal approach allows a more careful dissection of the mesorectum. In our study described in *chapter 7*, a case-matched analysis was performed for 25 (out of 312) patients who underwent completion TaTME (cTaTME) and 25 (out of 63) patients after conventional completion TME (cTME). Results showed that rectal perforation, which is known to be associated with local recurrence, occurred significantly more frequent in cTME compared to cTaTME, 28% and 4% respectively. The number of harvested lymph nodes was also higher after cTaTME than after cTME. Although operation time was longer in cTaTME patients, hospital stay was significantly longer after cTME. These results show that TaTME is a promising technique for completion radical surgery following local excision in patients with rectal cancer.



## Future perspectives

Although TaTME has been introduced as an alternative approach for laparoscopic surgery for rectal cancer patients, it remains uncertain whether this technique will become the standard treatment for these patients. In part, this is ascribable to the fact that TME surgery in general, currently performed by transanal, open, laparoscopic, robotic or combined approach, is associated with postoperative morbidity and mortality due to the extensiveness of the procedure depending on; tumour stage, tumour height, age and preoperative comorbidity. Reported severe postoperative outcomes such as faecal incontinence, urinary complaints, sexual dysfunction, stoma-related problems and anastomotic leakage are no exception and may result in poor social role and body image.[9-13]

Consequently, less invasive, organ sparing treatments such as local excision or even non-operative treatments using a wait-and-see approach following chemoradiotherapy have seen an increased interest. Even more so since achievement of pathological complete response (pCR) after chemoradiation (CRT) occurs in 15-25 percent; a result that is likely to be associated with decreased local and distant recurrence rates and improved survival.[14-16] Patients treated by a wait-and-see approach with a clinical complete response after neoadjuvant chemoradiotherapy, can avoid major surgery in approximately 60-70%.[17-19] Not surprisingly, taking this approach leads to better

functional outcomes and better 3-year colostomy-free survival rates compared to surgical resection.[17,20] Although disease-free survival is reported to be better after surgical resection, overall survival rates are comparable.[17,20,21] This suggests that with a wait-and-see approach major surgery can be avoided without compromising oncological outcomes. However, with a limited amount of literature gathered from small sample sizes, short follow-ups and retrospective studies, much of the information should be interpreted with caution. Moreover, clinical complete response does not always correspond with a pathological complete response due to both overstaging and understaging, regardless of the diagnostic test used (digital rectal examination, endoscopic ultrasound, MRI or CT).[22-25] Due to limited accuracy of the individual modalities, combining these tests is suggested in de literature.[26,27] Until consensus is reached on how to safely assess clinical (complete) response, a wait-and-see policy should only occur in rare cases after a thorough patient selection.

Another organ sparing procedure, currently used as primary treatment for low-risk early stage tumours, is local excision (TEM, TAMIS, transanal single port microsurgery (TSPM), endoscopic mucosal resection (EMR), endoscopic submucosal dissection (ESD), polypectomy).[28] When performing local excision after neoadjuvant therapy, overtreatment that may occur when performing TME surgery can be diminished and pathological response can be assessed accurately. The CARTS-study [29] reported data on TEM after chemoradiation in patients with tumour downsizing (ycT0-2). After TEM, patients with ypT0-1 had intensive follow-up for early detection; patients with ypT2-3 were to undergo completion total mesorectal excision (cTME). Fifty-one out of 55 patients completed CRT, of which 47 underwent TEM due to tumour downsizing. Thirty patients (55%) achieved pathological complete response or ypT1. This shows that local excision can be a safe alternative for TME in highly selected patients.

Nevertheless, for patients with intermediate risk of rectal cancer, completion TME is still required in addition to TEM surgery. As stated before, overtreatment in these cases might occur, but solely performing local excision could be insufficient due to the risk of lymph node involvement. The TESAR trial [28], will compare adjuvant chemoradiotherapy and completion TME for intermediate risk T1-2 rectal cancer following TEM without neoadjuvant therapy. They hypothesise that adjuvant chemoradiotherapy is non-inferior to TME in terms of local recurrence; and superior in terms of treatment related morbidity, functional outcome and quality of life.

Another recently started international multicentre trial (STAR-TREC) [30], will compare the wait-and-see policy or local excision after (chemo)radiotherapy with total mesorectal excision for early rectal cancer. Patients with T1-3bN0M0 <40mm rectal tumours will be randomised for TME surgery, CRT

(25x2Gy and capecitabine) or 5x5Gy radiotherapy. Patients in the latter two groups will, depending on the response after (chemo)radiotherapy, receive TME (poor response), wait-and-see (complete clinical response) or TEM (incomplete clinical response).

Aiming for increased rectal preserving treatments, these protocols seem promising. Rullier et al. [31] recently published data on outcomes for patients with stage T2-T3 rectal cancer with good clinical response to chemoradiotherapy, which were randomly assigned to TME or TEM. However, superiority of local excision over TME could not be proven because completion TME was frequently needed (35%), resulting in increased morbidity and side-effects. Careful patient selection for performing TEM instead of TME is therefore of the highest importance in order to decrease these numbers of completion surgery.

The variety of treatments currently used, demonstrates that - at time of publishing this thesis - there is no standard treatment for rectal cancer yet. When Heald initially introduced the 'invasive' total mesorectal excision in 1982, survival rates improved significantly.[32] However, as a result of continues innovation of oncological treatments by neoadjuvant therapy and enhanced surgical techniques, minimal invasive surgery without compromising oncological outcomes has gained position at the forefront of our treatment aspirations. Laparoscopic approach has only recently been proven to be superior over open TME in terms of short-term outcomes, and equal in terms of long-term outcomes.[33] However these treatments are often obsolete as soon as studies about these treatments are published, due to increasing advancements in medical techniques.



Transanal TME has proven to be safe and feasible in the early phase of implementation. Oncological outcomes compared to laparoscopic surgery will be researched in the international multicentre COLOR III trial, however it will take another couple of years before results of this study will become available.[34] The expectation is that TaTME will increase the quality of mesorectum with less percentage CRM involvement and eventually lower recurrence rates. On the contrary, robot-assisted TME surgery has gained wide interest and has shown to be non-inferior, but not superior, to laparoscopic TME in terms of perioperative outcomes, although conversion rate is reported to be lower.[35-37] The RESET trial, comparing open, laparoscopic, robot-assisted and transanal TME, may provide us with the answer to the question which surgical treatment should be the standard method of care.[36]

Nonetheless, in a world where technique is evolving as fast as it is and patients are gradually becoming more involved in shared-decision making, there may never be such a thing as 'one standard'. Instead, it is more likely that tailored treatment will increasingly become the norm. In

years to come, therefore, it is likely that the preferred treatment of rectal cancer, whether non operative, rectal preserving or TME surgery, will be determined based on preference and experience of the surgeon, patient characteristics and, last but not least, the patients' choice.

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